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Letter to the Editor

Response to Crump et al.

In their letter, Crump et al. purport to demonstrate that our "bottom–up" approach (Starr and Swenberg, 2013) "does not necessarily" bound low-dose cancer risk. Their demonstration is based on: (1) their speculation that the "true" dose–response relationship is sublinear and concave upward in the endogenous exposure range, and (2) faulty logic ostensibly implying that such nonlinearity guarantees that the linear assumption used in our "bottom–up" approach is not conservative.

Crump et al. provide no data to support their speculation, conceding that the "true" dose–response is actually unobservable near and below the endogenous exposure C_0. Instead, they simply assert without proof that such nonlinear behavior in the endogenous exposure range is "clearly plausible on biological grounds". However, it should be obvious that one can always construct a hypothetical dose–response relationship that will exceed any empirically-derived confidence bound on risk, including those that result from the standard top–down approach to risk assessment that has been the common practice in federal and state regulatory agencies for many years. This is not news, nor at all surprising. What is surprising is that Crump et al., who have been long-time proponents of low-dose linearity, would embrace a completely antithetical position, namely, dominant low-dose nonlinearity, with no supporting evidence whatsoever.

The critical question is this: what can be meaningfully inferred about potential cancer risks at and above the endogenous exposure C_0 from the limited tumor incidence data that are available? When we incorporated endogenous and exogenous formaldehyde adduct data into the standard top–down risk assessment approach and computed maximum likelihood estimates of low-dose nasal cancer risk to chronically exposed rats using Crump's Global82 multistage dose–response model fitting program (Howe and Crump, 1982) we obtained results very different from those shown in Crump et al.'s Fig. 1, where their hypothetical "true" sublinear dose–response relationship passes directly through the background risk (P_0) with a slope at C_0 and higher exposures that is far greater than our bottom–up bound on the slope, the ratio P_{0U}/C_{0L}.

As shown in our Fig. 1, the fitted multistage dose–response (green curve) is highly nonlinear and concave upward below C_0, but it is nevertheless extremely flat below C_0, as well as for a substantial distance above C_0. Furthermore, the fitted model actually under-predicts the observed risk at C_0, with most of the background risk at C_0 attributed to sources other than the endogenous formaldehyde adducts (the fitted model has a substantial intercept parameter).

Our Fig. 1 shows that at C_0, the slope of the bottom–up bound on added risk (red line) is greater (more than an order of magnitude greater) than the slope of the fitted multistage model. In addition, the bottom–up bound on the slope of added risk continues to exceed the slope of the added risks predicted by the fitted multistage model at adduct burdens up to and considerably beyond the 6.4 total formaldehyde-dG adducts per 10^7 dG (endogenous + steady-state exogenous) that are predicted to result from chronic 6 h/day 5 day/week inhalation exposures to 2 ppm formaldehyde. Our bound on added risk also exceeds, by a substantial margin, the fitted multistage model estimates of added risk up to the same total formaldehyde-dG adduct concentrations. These observations demonstrate clearly that it is Crump et al.'s logic, not ours, which is flawed.

We also wish to call readers' attention to the following pertinent facts: (1) our bottom–up approach explicitly incorporates uncertainty in the estimated background risk P_0 by replacing it with an upper confidence bound P_{0U} when that is appropriate, as it is here, with the very limited data on background rat nasal cancer risk that is available from chronic bioassays (Crump et al. either ignored, or do not seem to have noticed, this point despite considerable discussion of it in Starr and Swenberg (2013); (2) we recognized from the outset that the bottom–up bounding approach would not apply at sufficiently high exogenous doses, where nonlinear responses that amplify the carcinogenic response, such as accelerated cell proliferation, are expected, and indeed, have been demonstrated, to occur; and (3) our bottom–up approach to bounding low-dose cancer risk is a natural extension, to cases where endogenous exposure plays a significant role, of the model-free extrapolation approach put forward nearly a quarter of a century ago by Krewski et al. (1991).

Our bottom–up approach to bounding low-dose cancer risks is not a panacea, and hence may not always prove useful, but for cases where there is little or no empirical evidence of a positive dose–response at low exogenous exposure levels, we are confident that it provides a very useful "reality check" on conservative risk extrapolations from high-dose tumor data. Further details of the application of the bottom–up approach using tumor data in formaldehyde-exposed rats and humans will be provided in a manuscript that is currently in preparation.

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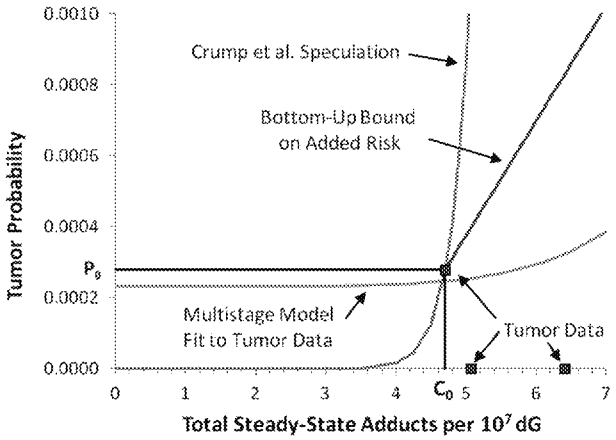

Fig. 1. Comparison of the "bottom–up" bound on added risk (red) with Crump et al.'s speculation about the "true" dose–response relationship (blue) and a maximum likelihood fit of the multistage dose–response model to nasal tumor data for formaldehyde-exposed rats (green).

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